



King's Research Portal

DOI:

[10.1177/1545968314533613](https://doi.org/10.1177/1545968314533613)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Fleming, M. K., Sorinola, I. O., Roberts-Lewis, S. F., Wolfe, C. D., Wellwood, I., & Newham, D. J. (2015). The effect of combined somatosensory stimulation and task specific training on upper limb function in chronic stroke: a double blind randomised controlled trial. *Neurorehabilitation and Neural Repair*, 29(2), 143-152.
<https://doi.org/10.1177/1545968314533613>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

The effect of combined somatosensory stimulation and task specific training on upper limb function in chronic stroke: a double blind randomised controlled trial

Melanie K Fleming, MSc^{1†}, Isaac O Sorinola, PhD^{2†*}, Sarah F Roberts-Lewis, BSc^{1,2}, Charles D Wolfe, PhD^{3,4}, Ian Wellwood, PhD^{3,4}, and Di J Newham, PhD¹

¹ Centre of Human and Aerospace Physiological Sciences, School of Biomedical Sciences, King's College London, UK

² Department of Physiotherapy, Division of Health and Social Care Research, School of Medicine, King's College London, UK

³ Department of Primary Care and Public Health Sciences, Division of Health and Social Care Research, School of Medicine, King's College London, UK

⁴ National Institute for Health Research Comprehensive Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK

† These authors contributed equally

*Corresponding Author

Isaac O Sorinola

Division of Health and Social Care Research

Guy's Campus, King's College London, London SE1 1UL

Email: isaac.2.sorinola@kcl.ac.uk

Ph: +44 (0) 207 848 8170

Fax: +44 (0) 207 848 6325

Word count: 4080

Tables: 2

Figures: 2

Abstract

Background: Somatosensory stimulation (SS) is a potential adjuvant to stroke rehabilitation, but the effect on function needs further investigation.

Objective: To explore the effect of combining SS with task specific training (TST) on upper limb function and arm use in chronic stroke survivors and determine underlying mechanisms.

Methods: In this double-blinded randomised controlled trial (ISRCTN 05542931), 33 patients (mean 37.7 months post-stroke) were block randomised to two groups: active or sham SS. They received 12 sessions of 2 hours of SS (active or sham) to all three upper limb nerves immediately before 30 minutes of TST. The primary outcome was the Action Research Arm Test (ARAT) score. Secondary outcomes were time to perform the ARAT, Fugl-Meyer Assessment score (FM), Motor Activity Log (MAL) and Goal Attainment Scale (GAS). Underlying mechanisms were explored using transcranial magnetic stimulation (TMS) stimulus-response curves and intracortical inhibition. Outcomes were assessed at baseline, immediately following the intervention (mean 2 days), 3 and 6 months (mean 96 & 190 days).

Results: The active group (n= 16) demonstrated greater improvement in ARAT score and time immediately post-intervention (between-group difference; $p < 0.05$), but not at 3 or 6 month follow ups ($p > 0.2$). Within-group improvements were seen for ARAT, GAS and MAL ($p < 0.05$), but there were no FM or TMS changes.

Conclusions: Long lasting improvements in upper limb function were observed following TST. Additional benefit of SS was seen immediately post treatment, but did not persist and the underlying mechanisms remain unclear.

Keywords: Stroke, Somatosensory Stimulation, Upper Limb, Task Specific Training, Rehabilitation, Transcranial Magnetic Stimulation

Introduction

Stroke is a leading cause of long term adult disability¹. Despite rehabilitation only 38% of people recover some dexterity by six months² and the majority have persistent disability³. Recovery could be facilitated by adjuvant strategies which facilitate brain plasticity⁴.

Somatosensory stimulation (SS) involves low intensity electrical stimulation of peripheral nerves, inducing paraesthesia without substantial motor output. Corticospinal excitability increases beyond the stimulation period in healthy adults⁵⁻⁷. In chronic stroke survivors, improvements in pinch strength⁸, functional task performance⁹ and motor training^{10,11} have been observed after a single session. Several studies have examined the cumulative effect of SS and motor training in chronic stroke¹²⁻¹⁴. McDonnell et al.¹³ found small improvements in hand dexterity, which were not accompanied by changes in corticospinal excitability. This study had a small sample size and a relatively short intervention (9 sessions) which may have limited the effect. Two studies trialled home-based SS with motor training^{12,14}. Dos Santos-Fontes et al.¹² found improvements in function only for the active stimulation group that appeared to persist for at least four months, whereas Sullivan et al.¹⁴ found no between-group differences. The main difference between the studies lies in the method of SS, as Dos Santos-Fontes et al. stimulated the median nerve whereas Sullivan et al. used a glove electrode to stimulate the hand. Nerve stimulation may be more effective at priming the motor system than non-specific hand stimulation. Simultaneously stimulating all of the forearm nerves may further improve the effectiveness of SS.

Our aim was to extend understanding of SS effectiveness in chronic stroke by combining stimulation of all three forearm nerves with task specific training (TST)¹⁵⁻¹⁷. We hypothesised that active stimulation would yield greater improvements than sham for functional ability

(Action Research Arm Test¹⁸), impairment (Fugl-Meyer Assessment Scale¹⁹) and arm use (Motor Activity Log²⁰) with associated changes in corticospinal excitability (Transcranial Magnetic Stimulation).

Methods

Participants

Thirty three participants (13 women, mean age 61.5 years, range 24-84) with first ever stroke ≥ 3 months duration (average 37.7 months, range 3-130) were included (Table 1). Time since stroke and stroke location were determined from medical records when possible (Table 1). In some cases only limited information regarding stroke location was available. Participants were recruited between July 2010-2012 from five National Health Service sites, the South London Stroke Register, stroke support groups and informal networks. All appointments were conducted in a laboratory at King's College London. Original inclusion criteria were; age >65 years, unilateral upper limb weakness, physically able to participate (including being ambulant and able to negotiate a flight of stairs with assistance), completed upper limb rehabilitation and the presence of motor evoked potentials (MEPs) in response to Transcranial Magnetic Stimulation (TMS) with the muscles at rest or pre-activated²¹. Exclusion criteria were; contraindications to TMS such as epilepsy or seizures, cardiac pacemakers or metal implants in the head, severe spasticity (Modified Ashworth Scale²² ≥ 4), dysphasia or cognitive dysfunction sufficient to limit ability to provide informed consent. Due to slow recruitment the inclusion criteria were amended after ~8 months to include participants 18-65 years, with contraindications to TMS (n= 4, sham) or who declined to have TMS (n= 1, active). All participants gave written informed consent and the study was

approved by the National Research Ethics committee. The study was registered as a randomised clinical trial (RCT); ISRCTN 05542931.

Experimental Design (Fig. 1)

Randomisation

In this double-blinded RCT (Fig. 1) block randomisation (up to 6 per group) was performed by the physiotherapist using coin toss. It was necessary to block-randomise to maintain blinding by ensuring that concurrent attendees were in the same group.

Intervention

The intervention was delivered three days per week for 12 sessions by a neurophysiotherapist (SRL). Each session contained 2 hours of SS (active or sham) immediately prior to 30 minutes of TST.

Somatosensory Stimulation

Somatosensory stimulation was applied to all three nerves of the affected forearm with three pairs of surface electrodes (13mm Ag/AgCl Biotabs, Unomedical, UK). Electrode positions for both groups were: (1) median nerve cathode at the cubital fossa perpendicular to the anterior joint line of the elbow, anode at the midpoint of the anterior joint line of the wrist proximal to the carpal tunnel; (2) radial nerve cathode anterior to the lateral epicondyle of the elbow, anode at the lateral border of the radius proximal to the anatomical snuff box; (3) ulnar nerve cathode at the medial epicondylar groove of the elbow, anode distal to the medial border of the ulna proximal to the pisiform bone.

The stimulator (Electro muscle stimulator HX K11, Harox Technologies, Serbia) delivered bursts of 10 Hz stimulation at 50% duty cycle (500 ms on and off). For active stimulation, intensities were set at $3\times$ sensory threshold (assessed for each nerve independently) to induce sensory paraesthesia without overt muscle contraction, and adjusted if required. Both groups could see a flashing light on the stimulator and a voltage indicator. The sham set up used severed connector leads to prevent stimulation. Participants were blinded to group allocation by being told that they might or might not feel the stimulation.

Task Specific Training

Both groups received standardised TST sessions which were divided into six discrete sections of five minutes: (1) stretching and warm up; (2) grasp; (3) grip; (4) pinch; (5) gross movements and (6) participant choice. The core sections (2-5) were based around tasks of the Action Research Arm Test (ARAT), practiced in a pseudo-randomised order. For example section 2 involved practice of a range of reach and grasp functional activities.

Section 1 comprised slow passive sustained stretches of the upper limb held for ~30 s and active head/shoulder movements. For the core sections, each task was deconstructed to work on constituent parts as required and whole task facilitation was individually progressed. Movements were progressed from passive, to active-assisted, active movements with verbal prompting and to resisted/complex exercises once repetitive active performance was achieved. Resistance or complexity were increased by additional weights, increased range of movement, closing the eyes or standing to challenge trunk stability. All variations were tailored daily to the individual.

The ‘participant’s choice’ exercise was chosen based on agreement between the participant and the therapist during the first session. Participants identified a functional activity which was important to them and they found difficult or impossible to perform with their affected upper limb and a goal²³ was agreed. Activities included: buttoning a shirt; carrying a cup; writing; self-feeding and using a light switch. These were diverse, reducing therapy standardisation, but reflecting therapy in clinical scenarios and improving relevance²⁴.

Assessments

Participants underwent two baseline assessments, one week apart (mean 7.9 days, range 5-20), to ensure stability. Post-intervention (P) assessments were immediately (P1; mean 2.4 days), 3 months (P2; mean 96 days) and 6 months (P3; mean 190 days) following the intervention. Assessments were conducted by a trained rater (MF) who was blinded to group allocation.

Clinical assessments included the ARAT¹⁸ and upper limb Fugl-Meyer Assessment (FM)¹⁹. Self-reported affected arm use was assessed with the Motor Activity Log (MAL)²⁰. Corticospinal excitability and intracortical inhibition were assessed for each hemisphere using TMS.

ARAT

This scores upper limb function from 0–57 (high = good function)¹⁸. All tasks were attempted and timed using a stopwatch. Participants were allowed up to 60 s for each task and 60 s recorded if they were unable to complete. A total score and time (ARAT_{time}) was calculated as well as times for each subsection (grasp, grip, pinch and gross).

MAL

According to standardised procedures²⁰ participants rated how much (amount of use (AOU)) and how well (quality of movement (QUAL)) they used their affected arm for 28 activities of daily living. An average score was calculated for the amount of use (MAL_{AOU}) and quality (MAL_{QUAL}) scales.

FM

The upper limb portion was used as a measure of impairment, scored from 0–66 (high = low impairment)¹⁹.

Goal Attainment Scale (GAS)

This was used in a standard manner^{25,26} to assess the outcome of the TST ‘participant choice’ activity. Weighted scores were attributed to individual goals according to task completion over the intervention period only.

TMS

Setup

Participants with cerebellar lesions (active n=1, sham n=2) were not included. Motor evoked potentials (MEPs) from ipsilesional (affected) and contralesional primary motor cortices (M1) were elicited using a flat figure-of-eight coil (70 mm diameter) with a pair of Magstim 200² stimulators connected through a BiStim module (Magstim Company, UK). The optimal position for evoking MEPs in the relaxed first dorsal interosseus (FDI) muscle was established each session and marked directly on the scalp to ensure consistent coil placement.

The resting motor threshold (RMT) was determined for each FDI²⁷ and a stimulus-response (SR) curve constructed from 10 stimuli at 5 intensities (90, 100, 110, 120 and 130 % RMT) in a random order (Signal 4.07, CED, UK). The intensities used for the first baseline were used for all subsequent sessions. For participants with an RMT $\geq 100\%$ maximum stimulator output (MSO), only contralesional M1 was tested (active n=3, sham n=4). For intracortical inhibition (SICI), the test stimulus (TS) was set at the intensity which produced an MEP ~50% of the participant's maximum MEP amplitude, the conditioning stimulus (CS) at 85% RMT and the interstimulus interval (ISI) at 2.5ms. Ten non-conditioned and ten conditioned stimuli were delivered in a random order (Signal 4.07, CED, UK).

MEP Analysis

Peak-to-peak MEP amplitude (mV) was determined using Signal 4.07 (CED, UK), and averaged for each intensity. For SICI, the average conditioned MEP amplitude was expressed as a percentage of the non-conditioned then % inhibition calculated by subtracting from 100 so that positive values indicated inhibition of the test response.

The slope of the linear portion of the SR curve was calculated using a least squares method. Slope values were excluded if the fit resulted in an R^2 value < 0.85 ($< 2.5\%$ of trials). The laterality index of linear slope was calculated using the following classic formula: $(\text{Slope}_{\text{ipsilesional}} - \text{Slope}_{\text{contralesional}}) / (\text{Slope}_{\text{ipsilesional}} + \text{Slope}_{\text{contralesional}})$. This yields a value between -1 and +1 where negative values indicate relatively reduced activity of the ipsilesional corticospinal pathway.

Data Analysis

The primary outcome measure was change in ARAT immediately post-intervention.

Following confirmation that the two baseline values were not statistically different (Paired t-test or Wilcoxon signed rank tests) the mean was used unless otherwise stated. For between-group comparisons change scores from baseline were calculated for ARAT, FM, MAL and GAS. For ARAT_{time} % change from baseline was used. For TMS the change in laterality index of SR curve linear slope was calculated and positive changes indicate normalising of the balance in corticospinal excitability. For SICI the change in % inhibition was calculated for each hemisphere. For within-group comparisons absolute scores were used for all assessments.

The number of participants achieving a minimum clinically important change (MCID) in the ARAT (5.7 points) and MAL (0.5 points)²⁸ was recorded.

Statistical Analysis

Based on a pilot study¹³ we estimated 34 participants (17 per group) would give 80% power (at 5% level) to detect a 5 point improvement in ARAT at P1.

Per-protocol analysis was used. After Kolmogorov-Smirnov tests, parametric statistics were used for normally distributed data which are presented as mean (SD) unless otherwise specified. Otherwise non-parametric statistics were used and data are presented as median (95% confidence interval (CI)) unless otherwise specified. Significance was set at $p < 0.05$ or $p < 0.017$ for multiple comparisons (Bonferroni correction).

Between-group

Independent samples t-tests or Mann Whitney U tests were used to test for differences between groups at baseline and for the change values at each post-intervention time-point.

Within-group

For normally distributed data, a group by time repeated measures analysis of variance (rmANOVA) was used. If a significant effect of time was found post-hoc pairwise comparisons were conducted (with Bonferroni correction).

For non-normally distributed data, Friedman tests were used to examine within-group effects across time. If significant, post-hoc Wilcoxon signed rank tests were used to test for differences from baseline at each post-intervention assessment (with Bonferroni correction).

MCID Analysis

The proportion of participants reaching the MCID in ARAT ($\Delta > 5.7$) or MAL ($\Delta > 0.5$) was compared across groups using Fisher Exact tests.

Regression analysis

For the active group, post-hoc regression analysis was performed. Potential predictor variables (resting MEP presence, baseline SR slope laterality index, ARAT, FM, MAS, duration of stroke and age) were entered stepwise into multivariate linear regression analysis with change scores for ARAT, FM and MAL_{AOU} at each post-intervention time-point as dependent variables.

Results

The intervention sessions were well attended (99.7%). Two participants (one per group) were lost to 3 and 6 month follow-ups (unrelated illness and Botox treatment for pre-existing spasticity) and one participant (sham group) failed to attend at 3 months due to unrelated illness, but did attend at 6 months. The sample size at each time-point is shown in Fig. 1. There were no serious adverse effects. Minor ones included dermatitis (n=11) at the site of the active SS electrodes which resolved spontaneously (n=9) or with prescribed steroid cream (n=2) and mild shoulder pain (sham n=2, active n=1). One participant developed short-term nausea and light-headedness during TMS which was discontinued (remaining in the study without TMS).

The mean sensory threshold for the active group was 0.72 mA (range 0.71–0.74) and the mean stimulation intensity was 2.09 mA (range 2.05–2.15) across all 3 nerves. There were no significant differences between the stimulation intensities used for the three nerves ($p=0.1$). Stimulation was well tolerated.

There were no differences between groups at baseline for any assessments unless specified.

ARAT

ARAT score

ARAT scores were not normally distributed ($p=0.01$). There was a difference between groups immediately post-intervention as ARAT score increased to a greater extent for the active group (Δ active: 3.5 (1.5 – 8.5), sham: 1.0 (-0.5 – 5.0); $p=0.031$; Table. 2). There were no between-group differences at P2 or P3 ($p>0.4$, Table 2).

Friedman tests revealed significant within-group changes for both groups (active: $p < 0.001$, sham: $p=0.028$; Table 2). Post-hoc comparisons showed improvements from baseline for the active group at P1 ($p=0.001$), P2 ($p=0.014$) and P3 ($p=0.004$). There was a non-significant tendency for improvement from baseline for the sham group at P1 ($p=0.031$), P2 ($p=0.027$) and P3 ($p=0.02$).

The number of participants with a change score exceeding MCID was higher in the active group at P1 (5 vs 2) and P2 (3 vs 1). However, Fisher exact tests revealed no significant differences between groups at any time-point ($p > 0.2$).

ARAT time

ARAT_{time} was not normally distributed ($p=0.001$). There was an improvement between baselines for the active group ($B1=263.0$ (192 – 467.5) s, $B2=192.2$ (123.0 – 440.2) s, $p < 0.05$), so baseline 2 was used to calculate % change for both groups. There was no difference between groups at baseline 2 ($p=0.26$).

There was a significant difference between groups for the % change in ARAT_{time} at P1 ($p=0.017$) with a greater reduction for the active group (Δ active: -27.9 (-41.8 – -10.3) %, sham: -9.5 (-25.7 – 0.2) %; Table 2). There were no differences at P2 or P3 ($p > 0.2$).

For the ARAT subcomponents there was a difference between groups for the % change in ARAT_{time} for grasp at P1 and pinch at P1 and P3 with the active group showing greater reduction ($p < 0.05$; Table 2).

Motor Activity Log

Amount of Use

Ratings were normally distributed ($p=0.2$). There were no differences between groups in the change in MAL_{AOU} at any assessment (P1: $p=0.946$, P2: $p=0.264$, P3: $p=0.079$; Table 2).

The GROUP (active, sham) by TIME (Baseline, P1, P2, P3) rmANOVA revealed a significant effect of time ($F_{2,3,63.9} = 7.679$, $p=0.001$) but no interaction ($F_{2,3,63.9} = 1.821$, $p=0.165$). Post-hoc pairwise comparisons indicated an increase in rating from baseline for P1 ($p=0.001$), P2 ($p=0.003$) and P3 ($p=0.002$).

The number of participants with a change score exceeding MCID was higher in the active group across all assessments (P1: 7 vs 6, P2: 8 vs 4, P3: 9 vs 4). However, Fishers exact tests revealed no significant differences between groups at any time-point (P1: $p=0.728$, P2: $p=0.264$, P3: $p=0.073$).

Quality

Ratings were normally distributed ($p=0.2$). There were no differences between groups in the change in MAL_{QUAL} at any assessment (P1: $p=0.474$, P2: $p=0.510$, P3: $p=0.375$; Table 2).

The GROUP (active, sham) by TIME (Baseline, P1, P2, P3) rmANOVA revealed a significant effect of time ($F_{3,81} = 3.428$, $p=0.021$) but no interaction ($F_{3,81} = 0.834$, $p=0.479$). Post-hoc pairwise comparisons indicated an increase in rating from baseline for P1 ($p=0.01$), but not P2 ($p=0.17$) or P3 ($p=0.027$).

FM

FM scores were normally distributed ($p=0.09$). There were no differences between groups for the change at any assessment (P1: $p=0.104$, P2: $p=0.750$, P3: $p=0.504$; Table 2).

The GROUP (active, sham) by TIME (Baseline, P1, P2, P3) rmANOVA revealed a tendency toward an effect of time ($F_{1,9,53.4} = 3.22$, $p=0.050$) but no interaction ($F_{1,9,53.4} = 0.82$, $p=0.59$).

Post-hoc pairwise comparisons showed an increase from baseline for P2 ($p=0.011$), but not P1 ($p=0.021$) or P3 ($p=0.032$).

GAS

GAS scores were not normally distributed ($p < 0.001$). There was a tendency for the change to be greater for the active group (Δ active: 20.0 (10.0 - 32.1), sham: 10.0 (0.0 - 20.0); $p=0.07$).

The within-group increase was significant for both groups (active $p=0.007$, sham $p=0.005$).

Transcranial Magnetic Stimulation

RMT

RMT was normally distributed for ipsilesional M1 ($p=0.055$) but not contralesional ($p=0.026$) so non-parametric statistics were used for both hemispheres. Ipsilesional M1 had a higher RMT than contralesional for both groups (ipsilesional active: 69 (49 - 96), sham: 77.5 (56.5 - 100); contralesional active: 50.25 (45 - 67.5), sham: 57 (44 - 69); active $p=0.008$, sham $p=0.009$). There were no between-group differences at any post-intervention time-point (all $p > 0.2$) and no within-group effects for either hemisphere (all $p > 0.4$).

Laterality Index of SR Curve linear slope

Laterality indices were not normally distributed ($p=0.008$). Baseline laterality index for active was -0.64 (-0.98 - -0.34) and -0.88 (-1 - -0.17) for sham. There were no differences between

groups for the change in laterality index at any post-intervention time-point (P1: $p=0.076$, P2: $p=0.603$, P3: $p=0.756$, Fig 2A) and no within-group effects (active $p=0.284$, sham $p=0.753$).

SICI

The % inhibition was normally distributed for ipsilesional hemisphere ($p=0.2$) but not contralesional ($p=0.018$) so non-parametric statistics were used for both.

Ipsilesional Hemisphere

There was a significant increase in % inhibition between baselines for the active group ($B1 = 12.4$ (-10.0 – 66.1) %, $B2 = 40.5$ (13.7 – 77.3) %; $p < 0.021$) so baseline 2 was used. There was no difference between groups at baseline 2 ($p=0.724$).

There was a tendency toward a significant between-group difference for the change in % inhibition at P2 which tended to reduce to a greater extent for the active group (Δ active = -64.4 (-92.0 – -1.2), sham = -10.4 (-46.2 – 79.8); $p=0.056$, Fig 2B). There were no between-group differences at P1 ($p=0.211$) or P3 ($p=0.792$).

Friedman tests indicated a significant within-group effect for active ($p=0.045$), but not sham ($p=0.564$). Post-hoc comparisons for the active group showed that % inhibition was significantly reduced at P2 compared with baseline ($p=0.013$) but not at P1 ($p=0.091$) or P3 ($p=0.074$). However at P2 it was noted that 6 participants (of 10) in the active group showed facilitation of the test response, rather than inhibition.

Contralesional Hemisphere

There were no differences between groups in the change in % inhibition at any assessment ($p > 0.3$, Fig. 2C) and no within-group effects ($p > 0.08$).

Regression analysis

Baseline FM predicted 30% of the variability in change in ARAT score at P1 ($F_{1,11} = 5.8$, $p < 0.05$). There were no other significant predictors of change in ARAT, FM or MAL_{AOU} following SS.

Discussion

Four weeks of combined SS and TST induced short-term improvements in ARAT that were greater than after TST alone. Despite the intensive nature of the study, adherence and follow-up rates were good. Both groups achieved their goals and increased self-reported amount of paretic arm use. However, these functional changes were not accompanied by significant modulations of corticospinal excitability.

Functional Improvements

SS combined with TST elicited greater improvements in function immediately post-intervention than TST alone. However this was a short term effect with differences between groups not persisting at three or six months. The study was powered to detect a 5-point change in ARAT immediately post-intervention based on the information available when the study commenced¹³ and adherence to the intervention was good. However, the anticipated effect may have been optimistic and as such the power was lower than expected at all time-points (P1=65, P2=16, P3=20 %). Despite this, the between-group difference at P1 was significant. There was also a within-group effect of time on ARAT score for both groups and a tendency toward an effect of time for FM, suggesting that TST was effective, but with

Bonferroni correction the improvements from baseline for ARAT were only significant for the active group, and for FM were only significant at 3 months. GAS scores improved for both groups suggesting that TST helped the participants to achieve their goals.

Previous studies¹²⁻¹⁴ have found mixed results with regard to SS specific changes in arm function. McDonnell et al.¹³ found no between-group differences in ARAT change after median nerve stimulation and TST. It may be that stimulation of all three forearm nerves in our study provided sufficient extra input for a difference in ARAT, at least transiently. However, Dos Santos-Fontes et al.¹² did find between-group differences in Jebsen Taylor Test (JTT)²⁹ performance in a home-based study involving daily SS of the median nerve with training. They had more frequent sessions, suggesting that SS dosage might be a significant factor needing further investigation. Additionally, impairment severity was less for Dos Santos-Fontes (FM range 48-64) compared to this study (22-61). In our study, baseline FM predicted 30% of the variability in change in ARAT following combined SS and TST, suggesting that SS may be more effective for those who can actively use the upper limb for motor practice. However, baseline ARAT was not a significant predictor and further investigation into the factors that affect response to SS is needed.

By recording the time taken to perform each ARAT task we attempted to capture any subtle improvements, particularly in the middle range where participants scored two out of three for most tasks. Consistent with ARAT score, the active group demonstrated a greater improvement in total time immediately post-intervention compared with sham, indicating that SS facilitated faster movement as well as overall score. This supports previous findings of improved time to perform tasks of the JTT following SS and training¹². Further analysis of time for the subcomponents showed that SS enhanced speed particularly for dextrous

movements, which may be explained by the stimulation of nerves to forearm muscles. Similarly, McDonnell et al.¹³ reported improved hand dexterity, although they did not find overall ARAT improvements with SS. Future work is needed to examine the validity and reliability of ARAT time measurement and to compare it with other time-based functional tests, e.g. JTT²⁹ or Wolf Motor Function Test³⁰.

Neurophysiological Mechanisms

The median laterality index was negative at baseline, demonstrating an imbalance in corticospinal excitability with relative under- and over-excitability of the ipsilesional and contralesional motor cortices respectively. This has been demonstrated in this population previously³¹. There were no between or within-group changes for the lateralisation of M1 excitability, so SS and TST were not associated with changes in cortical excitability. This is consistent with previous work¹³ and post-hoc power calculations indicate that we were adequately powered at the immediate post-intervention assessment (91 %), although not at the longer-term follow ups (power < 30 %). SS may improve function through mechanisms not assessed here, such as changes in motor programming. The lack of change in corticospinal excitability could potentially explain why the magnitude of ARAT improvement was less than we were expecting¹³ and why it did not persist.

Inhibition (SICI) within the ipsilesional hemisphere was reduced 3 months following active SS. A decrease in SICI following a single session of SS has been shown¹⁰, but to our knowledge this is the first study to demonstrate a longer-term effect following repeated SS and TST sessions. However, this must be interpreted with caution as many of the participants demonstrated facilitation of the test response rather than inhibition. Since we did not optimise the conditioning parameters for each participant it is possible that we were not specifically

targeting the intracortical network. However it is difficult to understand why this would be the case at P2 only. Further investigation is required with a larger sample before conclusions can be drawn.

Conclusions

SS combined with TST induces short term improvements in function, as measured by ARAT, compared with TST alone. However, the mechanisms underlying the effect of SS remain unknown.

Acknowledgements

We thank the Dunhill Medical Trust [grant number R102/0209] and the South London Clinical Local Research Network for financial support. C.D.A.W and I.W acknowledge financial support from the department of Health through the National Institute for Health Research (NIHR) Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

We are grateful to the participants for their enthusiastic involvement and to everyone who assisted with recruitment, particularly at the South London Stroke Register and the Stroke Research Network. Thank you to Dr McDonnell, University of Adelaide, for generously sharing pilot data for designing the study, Tony Christopher and Lindsey Marjoram for technical support and Professor Toby Prevost and Dr Kun Liu for statistical advice.

References

1. Wolfe CD. The impact of stroke. *Br Med Bull.* 2000;56(2):275-286.
2. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke.* Sep 2003;34(9):2181-2186.
3. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: results of a follow-up study. *Disabil Rehabil.* Aug 1999;21(8):357-364.
4. Pekna M, Pekny M, Nilsson M. Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke.* Oct 2012;43(10):2819-2828.
5. McKay D, Brooker R, Giacomini P, Ridding M, Miles T. Time course of induction of increased human motor cortex excitability by nerve stimulation. *Neuroreport.* Jul 19 2002;13(10):1271-1273.
6. Ridding MC, McKay DR, Thompson PD, Miles TS. Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. *Clin Neurophysiol.* Aug 2001;112(8):1461-1469.
7. Wu CW, van Gelderen P, Hanakawa T, Yaseen Z, Cohen LG. Enduring representational plasticity after somatosensory stimulation. *Neuroimage.* Oct 1 2005;27(4):872-884.
8. Conforto AB, Kaelin-Lang A, Cohen LG. Increase in hand muscle strength of stroke patients after somatosensory stimulation. *Ann Neurol.* Jan 2002;51(1):122-125.
9. Wu CW, Seo HJ, Cohen LG. Influence of electric somatosensory stimulation on paretic-hand function in chronic stroke. *Arch Phys Med Rehabil.* Mar 2006;87(3):351-357.
10. Celnik P, Hummel F, Harris-Love M, Wolk R, Cohen LG. Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. *Arch Phys Med Rehabil.* Nov 2007;88(11):1369-1376.
11. Sawaki L, Wu CW, Kaelin-Lang A, Cohen LG. Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. *Stroke.* Jan 2006;37(1):246-247.
12. Dos Santos-Fontes RL, Ferreiro de Andrade KN, Sterr A, Conforto AB. Home-Based Nerve Stimulation to Enhance Effects of Motor Training in Patients in the Chronic Phase After Stroke: A Proof-of-Principle Study. *Neurorehabil Neural Repair.* Mar 11 2013.
13. McDonnell MN, Hillier SL, Miles TS, Thompson PD, Ridding MC. Influence of combined afferent stimulation and task-specific training following stroke: a pilot randomized controlled trial. *Neurorehabil Neural Repair.* Sep-Oct 2007;21(5):435-443.
14. Sullivan JE, Hurley D, Hedman LD. Afferent stimulation provided by glove electrode during task-specific arm exercise following stroke. *Clin Rehabil.* Nov 2012;26(11):1010-1020.
15. Dobkin BH. Training and exercise to drive poststroke recovery. *Nat Clin Pract Neurol.* Feb 2008;4(2):76-85.
16. Hubbard IJ, Parsons MW, Neilson C, Carey LM. Task-specific training: evidence for and translation to clinical practice. *Occup Ther Int.* 2009;16(3-4):175-189.
17. Shepherd RB. Exercise and training to optimize functional motor performance in stroke: driving neural reorganization? *Neural Plast.* 2001;8(1-2):121-129.
18. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res.* 1981;4(4):483-492.
19. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med.* 1975;7(1):13-31.
20. Uswatte G, Taub E, Morris D, Light K, Thompson PA. The Motor Activity Log-28: assessing daily use of the hemiparetic arm after stroke. *Neurology.* Oct 10 2006;67(7):1189-1194.
21. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain.* Jan 2007;130(Pt 1):170-180.
22. Ashworth B. Preliminary Trial of Carisoprodol in Multiple Sclerosis. *Practitioner.* Apr 1964;192:540-542.

23. Hurn J, Kneebone I, Cropley M. Goal setting as an outcome measure: A systematic review. *Clin Rehabil.* Sep 2006;20(9):756-772.
24. Davis JZ. Task selection and enriched environments: a functional upper extremity training program for stroke survivors. *Top Stroke Rehabil.* Summer 2006;13(3):1-11.
25. Kiresuk T, Smith A, Cardillo J. *Goal attainment scaling: application, theory and measurement.* New York: Lawrence Erlbaum Associates; 1994.
26. Turner-Stokes L, Williams H. Goal attainment scaling: a direct comparison of alternative rating methods. *Clin Rehabil.* Jan 2010;24(1):66-73.
27. Rossini PM, Barker AT, Berardelli A, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol.* Aug 1994;91(2):79-92.
28. van der Lee JH, Beckerman H, Lankhorst GJ, Bouter LM. The responsiveness of the Action Research Arm test and the Fugl-Meyer Assessment scale in chronic stroke patients. *J Rehabil Med.* Mar 2001;33(3):110-113.
29. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. *Arch Phys Med Rehabil.* Jun 1969;50(6):311-319.
30. Wolf SL, Catlin PA, Ellis M, Archer AL, Morgan B, Piacentino A. Assessing Wolf motor function test as outcome measure for research in patients after stroke. *Stroke.* Jul 2001;32(7):1635-1639.
31. Talelli P, Greenwood RJ, Rothwell JC. Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. *Clin Neurophysiol.* Aug 2006;117(8):1641-1659.

Figure Captions.

Fig. 1. Trial profile

Fig 2. Box and whisker plot showing change in TMS measures (with outliers removed). A. Stimulus Response (SR) Curve lateralisation index. Positive changes indicate improved balance in excitability between hemispheres. B. % inhibition of ipsilesional primary motor cortex (M1). Negative values indicate reduction in short latency intracortical inhibition (SICI). There was a significant within group effect of time for the active group and SICI was lower at P2 than baseline ($p = 0.013$). C. % inhibition of contralesional M1. Positive values indicate increased SICI.

Tables

Table 1. Participant Characteristics.

	Active (n=16)	Sham (n=17)	<i>p</i>
Demographics			
Age, years	62.3 (35 – 82)	60.6 (24 – 84)	0.74 ^a
Gender, male	13 (81.3)	7 (41.1)	-
Clinical Characteristics			
Time since stroke, months	28.9 (3 – 130)	26.6 (4 – 126)	0.87 ^b
Affected arm, right	10 (62.5)	9 (52.9)	-
Ischaemic	13 (81.2)	14 (82.4)	-
Haemorrhage	3 (18.8)	3 (17.6)	-
Region			
Lacunar	10 (62.5)	7 (41.1)	-
MCA territory	4 (25.0)	7 (41.1)	-
Cerebellar	1 (6.3)	2 (11.8)	-
Unknown region	1 (6.3)	1 (5.9)	-
Stroke disability			
ARAT (max 57)	32.8 (10 – 43)	26.6 (9 – 49)	0.22 ^b
FM (max 66)	43.3 (22 – 60)	37.5 (23 – 59)	0.08 ^a
Barthel Index (max 20)	18.3 (14 – 20)	18.1 (15 – 20)	0.56 ^b
FAST (max 30)	24.8 (9 – 29)	24.4 (13 – 30)	0.95 ^b
MAS	1.3 (0 – 3)	1.3 (0 – 3)	0.96 ^b

Data are mean (range) or number (%). ^a Independent samples t-test, ^b Mann Whitney U tests between groups for baseline values. MCA = Middle Cerebral Artery, ARAT = Action Research Arm Test, FM = Fugl Meyer Upper Limb Assessment, FAST = Frenchay Aphasia Screening Test, MAS = Modified Ashworth Scale. There were no significant differences between groups at baseline for clinical characteristics or disability.

Table 2. Change from baseline

	Active			Sham		
	P1	P2	P3	P1	P2	P3
Δ ARAT Score						
Median (95 % CI)	3.5 (1.5 – 8.5)*†	2.5 (0.5 – 5.5)†	2.5 (1.5 – 5.5)†	1.0 (-0.5 – 5.0)	2.0 (0.5 – 4.0)	2.75 (0.0 – 4.5)
% Δ ARAT_{Time}						
Median (95 % CI)						
<i>Grasp</i>	-28.4 (-38.0 - -20.5)*	-23.2 (-35.9 - -11.5)	-29.1 (-44.0 - -5.0)	-2.2 (-26.6 – 0.0)	-14.5 (-28.5 – 0.0)	-11.9 (-41.8 - 0.0)
<i>Grip</i>	-27.8 (-40.6 - -11.9)	-10.7 (-36.2 – 1.1)	-23.7 (-32.4 - -0.8)	-3.7 (-23.4 – 0.0)	-19.9 (-22.7 – 0.0)	11.1 (-22.8 – 0.0)
<i>Pinch</i>	-25.4 (-55.5 - -7.3) *	-11.2 (-37.4 – 2.8)	-29.0 (-52.4 - -13.5)*	0.0 (-30.7 – 0.0)	0.0 (-32.9 – 0.0)	-7.2 (-32.2 – 0.0)
<i>Gross</i>	-18.4 (-64.7 - -0.61)	-21.0 (-37.3 – 2.0)	-21.1 (-49.7 – 10.2)	-9.6 (-35.7 – 0.9)	-19.2 (-46.3 – 0.5)	-19.6 (-42.4 – 0.6)
<i>Total</i>	-27.9 (-41.8 - -10.3)*	-8.5 (-35.5 – 7.5)	-21.2 (-38.0 - -2.9)	-9.5 (-25.7 – 3.0)	-8.9 (-29.0 – 0.09)	11.1 (-28.7 – 0.0)
Δ MAL Rating						
Mean (SD)						
<i>Amount of Use</i> ‡	0.48 (0.64)	0.54 (0.76)	0.69 (0.93)	0.46 (0.62)	0.26 (0.58)	0.21 (0.50)
<i>Quality</i> ‡	0.29 (0.56)	0.20 (0.66)	0.45 (0.75)	0.17 (0.30)	0.11 (0.47)	0.10 (0.63)
Δ FM Score						
Mean (SD)	2.5 (3.1)	2.5 (4.2)	2.8 (4.7)	0.6 (3.6)	2.0 (4.9)	1.4 (6.8)

CI = confidence interval. SD = standard deviation. * Significant difference between groups, $p < 0.05$ (Mann Whitney U test or independent samples t-test). †Difference from baseline (Wilcoxon Signed rank test) $p < 0.017$. ‡ significant effect of time (repeated measures analysis of variance). P 1 = immediate post-intervention, P2 = 3 month follow up, P3 = 6 month follow up assessment. Δ = change, ARAT = Action Research Arm Test, MAL = Motor Activity Log, FM = Fugl-Meyer Upper Limb Assessment.